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(54) ACTIVE OXYGEN SCAVENGER AND COMPOSITION CONTAINING THE SAME

(57)Abstract:
PURPOSE: To obtain the subject highly safe scavenger having activity to sufficiently scavenge active oxygen produced in vivo, and a composition containing this scavenger.
CONSTITUTION: This active oxygen scavenger is an extract from walnutshells. The scavenger is formulated in a composition such as a food or medicine to obtain the objective composition.

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JAPANESE [JP,07-069912,A]

CLAIMS DETAILED DESCRIPTION TECHNICAL FIELD PRIOR ART EFFECT OF THE INVENTION TECHNICAL PROBLEM MEANS OPERATION EXAMPLE CORRECTION OR AMENDMENT

[Translation done.]

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CLAIMS

[Claim(s)]
[Claim 1] The active oxygen elimination agent which consists of an extract of walnut husks.
[Claim 2] The active oxygen elimination agent according to claim 1 characterized by extracting said extract by one sort chosen from water, a methanol, ethanol, n-propyl alcohol, i-propyl alcohol, n-butyl alcohol, i-butyl alcohol, sec-butyl alcohol, t-butyl alcohol, and an acetone, or two sorts or more.
[Claim 3] The constituent containing an active oxygen elimination agent according to claim 1.

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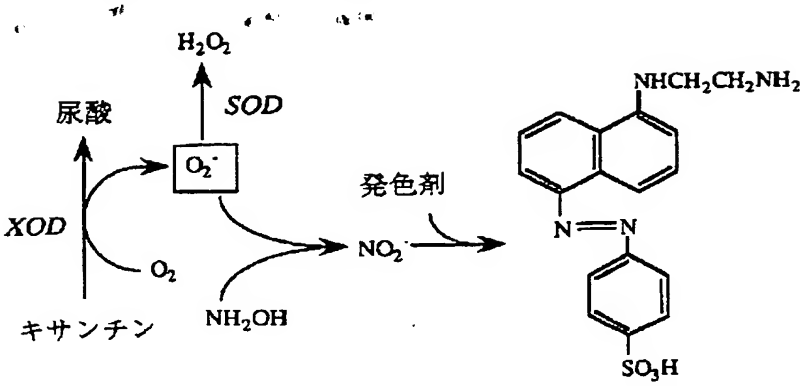
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the constituent which contains in detail the active oxygen elimination agent which consists of an extract of walnut husks, and this active oxygen elimination agent about the constituent containing an active oxygen elimination agent and this.
[0002]
[Description of the Prior Art] Generally as effect which active oxygen does to a living body Damage on the organization by bridge formation of a collagen fiber, and the partial cleavage of a DNA spiral and generating of a connective radical is mentioned. Inducement of allergic responses, such as aging of the skins as the result, such as Siwa and elasticity disappearance, or a living body, and bronchial asthma, and inducement of the inflammation by histamine emission. It is known that induction of the dementia by aggravation of diseases, such as damage on the smooth muscle in the myocardial infarction which is one of the ischemic diseases, and a liver failure, and destruction of brain tissue etc. will be caused. Furthermore, although the detailed cause and the device are unknown, they are a fact also with well-known active oxygen also participating also in the onset of rheumatism.
[0003] Therefore, it is very important to control generating of active oxygen in in the living body at the point which treats or prevents these diseases, and, for this reason, retrieval research of the drugs which have the operation which eliminates the active oxygen generated conventionally in the living body has been done widely.
[0004] For example, as what is used conventionally, the tocopherol (vitamin E) of lipophilicity, a water-soluble ascorbic acid (vitamin C), etc. are mentioned by the thing of the natural product origin as drugs which have such an operation, and BHT (3, 5-tert-butyl-4-hydroxytoluene), BHA (2(3)-tert-butyl-hydronalium KISHIANI reel), etc. are mentioned in a synthetic compound. However, about these drugs, there were problems that an active oxygen elimination operation was not enough and -- there arises carcinogenic misgiving -- by BHT of a synthetic compound, and BHA.
[0005] Moreover, recently, it asks for sufficient drug effect and sufficient safety, and many attempts in which the drugs which have an active oxygen elimination operation will be obtained from a crude drug extract are also made. For example, these all use an active oxygen elimination operation of a crude drug origin object for JP,60-224629,A, JP,61-24522,A, JP,2-193930,A, JP,2-243632,A, JP,2-264727,A, JP,3-153629,A, JP,3-221587,A, JP,4-69343,A, JP,4-202138,A, JP,4-247010,A, etc. However, in these crude drug extracts, although there was no problem in safety, when saying from the point of an active oxygen elimination operation, still sufficient thing was not obtained.
[0006] Furthermore, although the attempt which eliminates the active oxygen generated in the living body by prescribing 1 super oxide DESUMYUTAZE (SOD) of an enzyme for the patient has also been made, since SOD was protein, although the acquisition is not only difficult, but will be digested therefore, internal use was impossible and administration by injection was not that with which the half-life in blood is short and satisfaction goes, either.
[0007] On the other hand, about the husks of a walnut, knowledge with the grinding object useful as a scrub agent and its extract extractives are excellent in moistness as skin external preparations, and useful knowledge is known. However, it was not known that the extract extractives of these walnut husks have an active oxygen elimination operation, and drugs, food, etc. were made to contain this, and the attempt in which it used for various prevention and therapies of a disease which were mentioned above, prevention of aging, and an improvement was not carried out.
[0008]
[Problem(s) to be Solved by the Invention] This invention makes it a technical problem to offer the constituent which is made from the above-mentioned viewpoint, and has the operation which fully eliminates the active oxygen generated in the living body, and contains an active oxygen elimination agent and this with high safety.
[0009]
[Means for Solving the Problem] In order that this invention persons may solve the above-mentioned technical problem, while screening various matter by making an active oxygen elimination operation into an index That the fruit of the walnut which contains inside husks the partial saturation fats and oils which are easy to receive degradation by active oxygen can maintain internal partial saturation fats and oils at stability When it reasoned that it was because the defense mechanism over a certain active oxygen exists in outer husks and the walnut husks extract was covered over screening of an active oxygen elimination agent, it came to complete a header and this invention for the component which has the active oxygen elimination operation excellent in this walnut husks extract component existing.
[0010] That is, this invention relates to the constituent containing the active oxygen elimination agent and this which consist of an extract of walnut husks. Hereafter, this invention is explained to a detail.
[0011] The active oxygen elimination agent of active oxygen elimination agent this invention of <1> this invention consists of an extract of walnut husks. The walnut husks used for this invention are husks of the fruits of the Juglandaceae vegetation generally known, for example, walnut husks, such as demon GURUMI, MANSHUUGURUMI, and the Wall nuts, are mentioned.
[0012] The above-mentioned walnut husks take out the extract which contains the component which has an active oxygen elimination operation, and contains said component by extract, and it is used for them as an active oxygen elimination agent of this invention. Extract processings of walnut husks are approaches, such as continuous system and a batch type, and are performed the time of arbitration by maceration or digestion with a conventional method. For example, walnut husks are pulverized finely and it extracts by being immersed by one - three days, or the boiling temperature of an extracting solvent at a room temperature to an extracting solvent for 1 hour to 5 hours. Then, except for extract residue, reduced pressure or an ultrafiltration is performed from an extract, and an extract is condensed, or [furthermore, / distilling off an organic solvent completely and hardening by drying if needed,] -- or it freeze-dries.
[0013] As a solvent used for such an extract, although water and various organic solvents are mentioned, one sort chosen from

water, a methanol, ethanol, n-propyl alcohol, i-propyl alcohol, n-butyl alcohol, i-butyl alcohol, sec-butyl alcohol, t-butyl alcohol, and an acetone especially in this invention or two sorts or more are desirable.
[0014] The constituent of constituent this invention containing the active oxygen elimination agent of <2> this inventions blends the above-mentioned active oxygen elimination agent according to a conventional method, for example, drugs, food, etc. are mentioned.
[0015] Although especially a pharmaceutical form is not limited when pharmaceutical-preparation-izing it, using the active oxygen elimination agent of this invention as drugs, according to the usual approach,-izing can be carried out [pharmaceutical form] with the arbitration component usually used by drugs, such as an excipient, a binder, disintegrator, lubricant, a coloring agent, corrigent, an odor-masking agent, an extending agent, and coating, to various pharmaceutical preparation usually used, such as injections, powder, a granule, a tablet, a capsule, and liquids and solutions.
[0016] although it changes with the class of disease, a symptom, a patient's age, weights, etc. about the dose of the above-mentioned drugs -- an adult -- it is appropriate for one person to administer 10mg - 1000mg orally in 1 time thru/or several steps as an amount of the extract of per day and walnut husks, or to prescribe 5mg - 500mg for the patient by injection. As a medication method of injections, intravenous administration, intraarterial administration, the administration in a portal vein, intraperitoneal administration, intramuscular administration, subcutaneous administration, etc. are mentioned.
[0017] It can blend with various food with the arbitration component usually used with food, without minding especially, when blending the active oxygen elimination agent of this invention with food. If it illustrates, the staple food, such as confectionary, such as a candy, and GUMI and jelly, drinks like juice, and a pan, etc. will be mentioned. Although loadings change with classes of food, in order to acquire sufficient active oxygen elimination effectiveness, without spoiling the taste of food, its 0.1 - 10 % of the weight is desirable.
[0018] In addition, since walnuts are edible fruits, the extract of walnut husks can expect to excel in safety.
[0019]
[Function] The constituent containing the active oxygen elimination agent of this invention and this work effectively to the improvement of living body aging , such as a therapy of various illnesses , such as ischemic diseases , such as the inflammation and the senile dementia it be suppose that active oxygen be involve according to the active oxygen elimination operation which be excellent in the walnut husks extract which be the active principle as mention above , and myocardial infarction , or an allergic disease , a liver failure , and rheumatism , and the skin .
[0020] Moreover, the constituent containing the active oxygen elimination agent of this invention and this can be used effectively also because of prevention of the above-mentioned illness or living body aging. This is because the active oxygen which generated the component which has an active oxygen elimination operation by making it exist beforehand in the living body in the living body can be eliminated quickly and can be detoxified.
[0021]
[Example] Below, the example of this invention is explained. First, the example of the active oxygen elimination agent of this invention is explained.
[0022]
[Example 1] After having pulverized finely 500g of walnut husks of demon GURUMI, adding 5l. water to this and carrying out heating churning at 105 degrees C for 2 hours, it freeze-dried having filtered, having removed residue and having covered 2 ****s of obtained filtrate, and the walnut husks extract of demon GURUMI was obtained as 4.9g brown powder. This was made into the active oxygen elimination agent as it was.
[0023]
[Example 2] After having pulverized 500g of walnut husks of MANSHUUGURUMI finely, adding 5l. of equivalent mixed liquor of a methanol and n-butyl alcohol to this and performing churning, heating, and reflux for 2 hours, it filtered, residue was removed, vacuum concentration of the obtained filtrate was carried out, and 5.3g was obtained for the walnut husks extract of MANSHUUGURUMI as a viscosity nature liquid. This was made into the active oxygen elimination agent as it was.
[0024]
[Example 3] After having pulverized finely 500g of walnut husks of the Wall nuts, adding 5l. of acetone water solutions to this 50% and performing churning, heating, and reflux for 2 hours, it filtered, residue was removed and vacuum concentration of the obtained filtrate was carried out. Furthermore, freeze-drying processing of this concentrate was carried out over 48 hours, and the walnut husks extract of the Wall nuts was obtained as 5.1g being amorphous. This was made into the active oxygen elimination agent as it was.
[0025] About the active oxygen elimination agent obtained in <evaluation of active oxygen elimination agent> above-mentioned each example, evaluation about safety, an active oxygen elimination operation and aging, a liver failure, and the effectiveness over the allergosis was performed.
[0026] (1) Intraperitoneal [of the 5 weeks old ICR male mouse (weights 25-30g) of every two acute toxicity test 1 groups] was medicated with what dissolved the active oxygen elimination agent obtained in the example 1 in the physiological saline at a rate of 500 mg/kg, 1000 mg/kg, and 2000 mg/kg, respectively, and life and death were judged 14 days after. Consequently, the mouse survived also in said which dose and it was checked that a fifty percent lethal dose value is 2000mg/kg or more. It is clear that the active oxygen elimination agent of this invention excels this in safety.
[0027] (2) Measurement of an active oxygen elimination operation (in vitro)
Based on the reaction formula shown in ** 1, the yield of O2- which was made to generate the superoxide anion (O2-) which is one of the active oxygen by the xanthin-xanthine oxidase (XOD) system, and was generated was measured by the nitrous-acid method, this value was amended with the xanthine oxidase inhibition activity value, and the active oxygen elimination operation value was calculated.
[0028]
[Formula 1]



[0029] 0.1ml of active oxygen elimination agent water solutions which contain the active oxygen elimination agent obtained in each above-mentioned example at a 500microg [/ml] rate could be added to 65mM potassium dihydrogen phosphate, 35mM sodium borate, 0.2ml (henceforth the buffer solution A) of 0.5mMEDTA disodium water solutions, 0.2ml of 0.5mM xanthin solutions, 0.1ml of 10mM hydroxylamine-hydrochloride water solutions, and the mixed liquor of 0.2ml of pure water, they were agitated, and were used as test fluid. Similarly, the solution of the control which used 0.1ml of pure water instead of the active oxygen elimination agent was produced.
[0030] After adding 0.2ml of buffer solutions A which contain xanthine oxidase by 1microl. [/ml] concentration and agitating them in each above-mentioned test fluid and a control solution, the incubation was carried out at 37 degrees C for 30 minutes. 0.2ml of buffer solutions A which do not contain xanthine oxidase in the test fluid and the control solution which were adjusted like the above as a blank was added, and the solution processed like the above was prepared.
[0031] Thus, after adding a 30microMN-1-naphthyl ethylenediamine hydrochloride, 3mM sulfanilic acid, and 2ml of 25% glacial-acetic-acid mixtures to each of each obtained solution and leaving it at a room temperature for 30 minutes, about each solution, the yield of active oxygen was measured with the absorbance in 550nm, and the yield of a uric acid was measured with the absorbance of 295nm.
[0032] Based on the following formulas, the active oxygen elimination activity value was computed using the acquired value. A result is shown in Table 2.
[0033] < active oxygen elimination activity Formula > active oxygen incidence-rate =[for which it asks The notation in (A550-3-A550-4) / (A550-1-A550-2)]x100 uric-acid yield =[(A295-3-A295-4)/(A295-1-A295-2)] x100 active-oxygen elimination activity =100-(active oxygen incidence-rate / uric-acid yield) x100, however a formula It considers as the value of the absorbance of each solution adjusted on the conditions shown in Table 1.
[0034]
[Table 1]

測定波長 (nm)		キサンチンオキシダーゼ	
		存在下	非存在下
550 (活性酸素量)	コントロール 試 験 液	A_{550-1} A_{550-3}	A_{550-2} A_{550-4}
295 (尿酸量)	コントロール 試 験 液	A_{295-1} A_{295-3}	A_{295-2} A_{295-4}

[0035]
[Table 2]

	活性酸素消去活性値 (%)
実施例1の活性酸素消去剤	67. 1
実施例2の活性酸素消去剤	66. 2
実施例3の活性酸素消去剤	67. 5

It is clear from the above result that the active oxygen elimination agent of this invention has the outstanding active oxygen elimination operation.
[0036] (3) Measurement of an active oxygen elimination operation (in vivo)
After performing blood collecting from a 35-weeks old ICR system MCH male mouse (weights 30-40g), the active oxygen elimination agent obtained in the example 1 was administered orally to this mouse at a rate of 1000 mg/kg. It collected blood after [of administration] 30 minutes, and 2 hours and 5 hours after. The blood serum was picked out from the blood which collected blood with the above-mentioned monograph affair according to centrifugal separation, this was diluted with the buffer

solution A 10 times, and active oxygen elimination activity was measured by the same approach as the trial of the above (2). A result is shown in Table 3.

[0037]

[Table 3]

	活性酸素消去活性値（%）
投与前	47.8 ± 15.4
投与30分後	62.9 ± 10.9
2時間後	49.6 ± 7.6
5時間後	58.4 ± 4.5

It is clear for the active oxygen elimination agent of this invention to shift into blood promptly by internal use, and to maintain that effectiveness from this result, for a long time.

[0038] (4) 40 5 weeks old Wister system feminity rats of examination of the effectiveness over aging and a hepatopathy were divided into the appearance which does not have dispersion in weight at four groups, said pellet was made to take in the usual pellet (F2 feed, made in the Funabashi farm) in other three groups, and the active oxygen elimination agent of each example was bred [at one group / the pellet] for 1% of the weight of the blended thing for 24 months to it, respectively. In addition, it enabled it to take in a pellet and water freely to a rat during an experiment.

[0039] After 24-month breeding, it slaughtered, after extracting blood from the rat of each group. Then, the existence of an appearance was observed about disappearance of disseminated depilation, the plumping plasmotomy of the connective tissue under epidermis, sebaceous gland, and a sudoriferous gland as an evaluation index of aging about the rat of each group.

[0040] Furthermore, these rats were dissected, liver was extracted and evaluation about a hepatopathy was performed by observing under a microscope as an upper pathology sample of macro-scopic observation. Moreover, although it reacted easily with unsaturated fatty acid in the living body and peroxylipid was produced when active oxygen occurred in the living body, the active oxygen elimination effectiveness in each organ was evaluated by measuring the amount of peroxylipid which carried out in this way and was produced to each part of the inside of the body (inside of a blood serum, a brain, and liver) by the TBA method.

[0041] A result is shown [amount / of peroxylipid] in Table 4 as the number of appearance animals about other evaluation criteria as the average of ten animals.

[0042]

[Table 4]

		実施例1	実施例2	実施例3	コントロール
過酸化脂質量	血清中	11	10	10	18
	脳中	24	25	23	27
	肝臓中	29	29	27	36
＜老化の評価＞					
散在性脱毛		0	0	0	3
表皮下の結合組織の膨化断裂		0	0	0	4
脂腺、汗腺の消失		0	0	0	2
＜肝障害の評価＞					
肝臓への脂肪沈着		0	0	0	6
肝臓小葉への炎症細胞の湿潤		0	0	0	4
萎縮肝細胞		0	0	0	2

In each organ in the living body, it is clear the active oxygen elimination agent's of this invention to have controlled generation of peroxylipid well by eliminating active oxygen, and to have prevented a living body's aging, and to have prevented the failure of liver.

[0043] (5) According to the guinea pig maximization test method of examination KURIGUMAN of effectiveness to the allergosis, evaluation to an allergic inducement reaction was performed using the cinnamaldehyde which is the sensitizer.

[0044] The following experiments were conducted having made said pellet take in freely 1% of the weight of the thing and water which were blended for the active oxygen elimination agent of each example in other three groups, and breeding a usual pellet (F2 feed, made in the Funabashi farm) and water in them at two groups (among these, one group control group) of the guinea pig of every one groups [8-10], respectively.

[0045] Intradermal injection of 4 times, 1% cinnamaldehyde liquid paraffin solution, the equivalent mixed liquor of Freund's complete adjuvant, 1% cinnamaldehyde liquid paraffin solution, and the 0.05ml of the Freund's complete adjuvant was carried out to the guinea pig of each above-mentioned group except the guinea pig of a control group every two days at every two places of

every regions of back. Furthermore, from the injection opening day, the closed patch of what applied the cinnamaldehyde liquid paraffin solution to the putt section of an adhesive bandage 1% was carried out, and dermal administration was also performed at least in the period by the injection end date, and the above-mentioned injection section at coincidence.
[0046] The regions of back of all guinea pigs were shaved after two weeks, injection and a closed patch end date, dermal administration of each cinnamaldehyde liquid paraffin solution of 0.01%, 0.05%, 0.1%, 0.5%, and 1% concentration was carried out by the approach of carrying out a closed patch like the above for 24 hours, and the inducement reaction was seen. The Japanese Dermatological Association this country patch test criteria shown below were used for the criteria of evaluation. A result is shown in Table 5.
[0047] - : Adiaphorous ** : False positive reaction + : Positive reaction ++ : Reaction accompanied by an edema [0048]
[Table 5]

		実施例１	実施例２	実施例３	通常飼料	ｺﾝﾄﾛｰﾙ群
0．01％	－	4／8	4／10	5／9	3／10	9／9
	±	4／8	6／10	4／9	4／10	0／9
	＋	0／8	0／10	0／9	3／10	0／9
	＋＋	0／8	0／10	0／9	0／10	0／9
0．05％	－	4／8	4／10	5／9	2／10	9／9
	±	4／8	6／10	4／9	3／10	0／9
	＋	0／8	0／10	0／9	5／10	0／9
	＋＋	0／8	0／10	0／9	0／10	0／9
0．1％	－	2／8	2／10	3／9	0／10	9／9
	±	4／8	5／10	6／9	4／10	0／9
	＋	2／8	3／10	0／9	5／10	0／9
	＋＋	0／8	0／10	0／9	1／10	0／9
0．5％	－	0／8	0／10	0／9	0／10	9／9
	±	5／8	6／10	8／9	3／10	0／9
	＋	3／8	4／10	0／9	5／10	0／9
	＋＋	0／8	0／10	1／9	2／10	0／9
1％	－	0／8	0／10	0／9	0／10	5／9
	±	4／8	5／10	7／9	0／10	4／9
	＋	4／8	4／10	1／9	5／10	0／9
	＋＋	0／8	1／10	1／9	5／10	0／9

The active oxygen elimination agent of this invention has controlled the good allergic inducement reaction so that clearly from this result.
[0049] Next, the example of constituents, such as food, drugs, etc. containing the active oxygen elimination agent obtained in the above-mentioned example, is explained. In addition, especially all the things in which the loadings used for below do not have a notice are the weight sections.
[0050]
[Examples 4-6] The heating dissolution of the A component was carried out at 150 degrees C among the candy table 6, after casting what made B component homogeneity after addition and churning, it cooled and the candy was manufactured [after cooling at 120 degrees C].
[0051]
[Table 6]

成分		配合量		
		実施例４	実施例５	実施例６
A	砂糖	５８．０	６７．０	６７．０
	水飴	３０．０	３０．０	３０．９
B	クエン酸	１．０	１．０	１．０
	実施例１の活性酸素消去剤	１０．０	－	－
	実施例２の活性酸素消去剤	－	１．０	－
	実施例３の活性酸素消去剤	－	－	０．１
	香料	１．０	１．０	１．０

[0052]
[Example 7] B component which the heating dissolution was carried out [component] and carried out the swelling dissolution of the A component of the GUMI table 7 separately at 110 degrees C was added, further, C component was added and it slushed into the mold, and after neglect, it removed from the mold and GUMI was manufactured one whole day and night.
[0053]
[Table 7]

成分		配合量
A	砂糖	４０．０
	水飴	４５．０
B	ゼラチン	８．０
C	クエン酸	２．０
	実施例３の活性酸素消去剤	４．０
	香料	１．０

[0054]
[Example 8] the component of the juice table 8 — good — agitating — a solution — carrying out — sterilization and aseptic — it sealed and juice was manufactured.
[0055]
[Table 8]

成分	配合量
リンゴ果汁	９８．０
実施例１の活性酸素消去剤	２．０

[0056]
[Example 9] The component of the hot cake table 9 was often mixed, it roasted with the frying pan which oiled, and the hot cake was created.
[0057]
[Table 9]

成　　分	配　合　量
ホットケーキミックス（市販）	２４０ｇ
牛　　乳	１８０ｍｌ
全　　卵	２個
実施例２の活性酸素消去剤	５ｇ

[0058]
[Example 10] A component of the granule table 10 was often mixed, and in addition, it corned gradually, carrying out kneading of the B component melted in the ethanol water solution 20 100ml% at this. this — 40 degrees C -- 2 day-and-night ventilation desiccation — carrying out — screening -- the particle size regulation was carried out and it considered as the granule.
[0059]
[Table 10]

成　　分		配　合　量
A	乳　　糖	４５
	デキストラン	４５
	実施例１の活性酸素消去剤	５
B	ヒドロキシプロピルセルロース	５

[0060]
[Example 11] The component of the injections table 11 was dissolved, and it filtered, and sterilized, and into ampul, aseptic was carried out, and it enclosed, and considered as injections.
[0061]
[Table 11]

成　　分	配　合　量
塩化ナトリウム	０．９
実施例３の活性酸素消去剤	０．１
精　製　水	９９．０

[0062]
[Effect of the Invention] Its safety is high, and since the constituent containing the active oxygen elimination agent of this invention and this has the outstanding active oxygen elimination operation, it is effective in prevention of the allergosis in which active oxygen participates, and a hepatopathy, and prevention of a therapy and living body aging.

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TECHNICAL FIELD

[Industrial Application] This invention relates to the constituent which contains in detail the active oxygen elimination agent which consists of an extract of walnut husks, and this active oxygen elimination agent about the constituent containing an active oxygen elimination agent and this.

[Translation done.]

PRIOR ART

[Description of the Prior Art] Generally as effect which active oxygen does to a living body Damage on the organization by bridge formation of a collagen fiber, and the partial cleavage of a DNA spiral and generating of a connective radical is mentioned. Inducement of allergic responses, such as aging of the skins as the result, such as Siwa and elasticity disappearance, or a living body, and bronchial asthma, and inducement of the inflammation by histamine emission, It is known that induction of the dementia by aggravation of diseases, such as damage on the smooth muscle in the myocardial infarction which is one of the ischemic diseases, and a liver failure, and destruction of brain tissue etc. will be caused. Furthermore, although the detailed cause and the device are unknown, they are a fact also with well-known active oxygen also participating also in the onset of rheumatism.
[0003] Therefore, it is very important to control generating of active oxygen in in the living body at the point which treats or prevents these diseases, and, for this reason, retrieval research of the drugs which have the operation which eliminates the active oxygen generated conventionally in the living body has been done widely.
[0004] For example, as what is used conventionally, the tocopherol (vitamin E) of lipophilicity, a water-soluble ascorbic acid (vitamin C), etc. are mentioned by the thing of the natural product origin as drugs which have such an operation, and BHT (3, 5-tert-butyl-4-hydroxytoluene), BHA (2(3)-tert-butyl-hydronalium KISHIANI reel), etc. are mentioned in a synthetic compound. However, about these drugs, there were problems that an active oxygen elimination operation was not enough and -- there arises carcinogenic misgiving -- by BHT of a synthetic compound, and BHA.
[0005] Moreover, recently, it asks for sufficient drug effect and sufficient safety, and many attempts in which the drugs which have an active oxygen elimination operation will be obtained from a crude drug extract are also made. For example, these all use an active oxygen elimination operation of a crude drug origin object for JP,60-224629,A, JP,61-24522,A, JP,2-193930,A, JP,2-243632,A, JP,2-264727,A, JP,3-153629,A, JP,3-221587,A, JP,4-69343,A, JP,4-202138,A, JP,4-247010,A, etc. However, in these crude drug extracts, although there was no problem in safety, when saying from the point of an active oxygen elimination operation, still sufficient thing was not obtained.
[0006] Furthermore, although the attempt which eliminates the active oxygen generated in the living body by prescribing 1 super oxide DESUMYUTAZE (SOD) of an enzyme for the patient has also been made, since SOD was protein, although the acquisition is not only difficult, but will be digested therefore, internal use was impossible and administration by injection was not that with which the half-life in blood is short and satisfaction goes, either.
[0007] On the other hand, about the husks of a walnut, knowledge with the grinding object useful as a scrub agent and its extract extractives are excellent in moistness as skin external preparations, and useful knowledge is known. However, it was not known that the extract extractives of these walnut husks have an active oxygen elimination operation, and drugs, food, etc. were made to contain this, and the attempt in which it used for various prevention and therapies of a disease which were mentioned above, prevention of aging, and an improvement was not carried out.

[Translation done.]

* NOTICES *

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EFFECT OF THE INVENTION

[Effect of the Invention] Its safety is high, and since the constituent containing the active oxygen elimination agent of this invention and this has the outstanding active oxygen elimination operation, it is effective in prevention of the allergosis in which active oxygen participates, and a hepatopathy, and prevention of a therapy and living body aging.

[Translation done.]

* NOTICES *

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] This invention makes it a technical problem to offer the constituent which is made from the above-mentioned viewpoint, and has the operation which fully eliminates the active oxygen generated in the living body, and contains an active oxygen elimination agent and this with high safety.

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MEANS

[Means for Solving the Problem] In order that this invention persons may solve the above-mentioned technical problem, while screening various matter by making an active oxygen elimination operation into an index That the fruit of the walnut which contains inside husks the partial saturation fats and oils which are easy to receive degradation by active oxygen can maintain internal partial saturation fats and oils at stability When it reasoned that it was because the defense mechanism over a certain active oxygen exists in outer husks and the walnut husks extract was covered over screening of an active oxygen elimination agent, it came to complete a header and this invention for the component which has the active oxygen elimination operation excellent in this walnut husks extract component existing.
[0010] That is, this invention relates to the constituent containing the active oxygen elimination agent and this which consist of an extract of walnut husks. Hereafter, this invention is explained to a detail.
[0011] The active oxygen elimination agent of active oxygen elimination agent this invention of <1> this invention consists of an extract of walnut husks. The walnut husks used for this invention are husks of the fruits of the Juglandaceae vegetation generally known, for example, walnut husks, such as demon GURUMI, MANSHUUGURUMI, and the Wall nuts, are mentioned.
[0012] The above-mentioned walnut husks take out the extract which contains the component which has an active oxygen elimination operation, and contains said component by extract, and it is used for them as an active oxygen elimination agent of this invention. Extract processings of walnut husks are approaches, such as continuous system and a batch type, and are performed the time of arbitration by maceration or digestion with a conventional method. For example, walnut husks are pulverized finely and it extracts by being immersed by one - three days, or the boiling temperature of an extracting solvent at a room temperature to an extracting solvent for 1 hour to 5 hours. Then, except for extract residue, reduced pressure or an ultrafiltration is performed from an extract, and an extract is condensed. or [furthermore, / distilling off an organic solvent completely and hardening by drying if needed,] — or it freeze-dries.
[0013] As a solvent used for such an extract, although water and various organic solvents are mentioned, one sort chosen from water, a methanol, ethanol, n-propyl alcohol, i-propyl alcohol, n-butyl alcohol, i-butyl alcohol, sec-butyl alcohol, t-butyl alcohol, and an acetone especially in this invention or two sorts or more are desirable.
[0014] The constituent of constituent this invention containing the active oxygen elimination agent of <2> this inventions blends the above-mentioned active oxygen elimination agent according to a conventional method, for example, drugs, food, etc. are mentioned.
[0015] Although especially a pharmaceutical form is not limited when pharmaceutical-preparation-izing it, using the active oxygen elimination agent of this invention as drugs, according to the usual approach,-izing can be carried out [pharmaceutical form] with the arbitration component usually used by drugs, such as an excipient, a binder, disintegrator, lubricant, a coloring agent, corrigent, an odor-masking agent, an extending agent, and coating, to various pharmaceutical preparation usually used, such as injections, powder, a granule, a tablet, a capsule, and liquids and solutions.
[0016] although it changes with the class of disease, a symptom, a patient's age, weights, etc. about the dose of the above-mentioned drugs — an adult — it is appropriate for one person to administer 10mg - 1000mg orally in 1 time thru/or several steps as an amount of the extract of per day and walnut husks, or to prescribe 5mg - 500mg for the patient by injection. As a medication method of injections, intravenous administration, intraarterial administration, the administration in a portal vein, intraperitoneal administration, intramuscular administration, subcutaneous administration, etc. are mentioned.
[0017] It can blend with various food with the arbitration component usually used with food, without minding especially, when blending the active oxygen elimination agent of this invention with food. If it illustrates, the staple food, such as confectionary, such as a candy, and GUMI and jelly, drinks like juice, and a pan, etc. will be mentioned. Although loadings change with classes of food, in order to acquire sufficient active oxygen elimination effectiveness, without spoiling the taste of food, its 0.1 - 10 % of the weight is desirable.
[0018] In addition, since walnuts are edible fruits, the extract of walnut husks can expect to excel in safety.

[Translation done.]

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OPERATION

[Function] The constituent containing the active oxygen elimination agent of this invention and this work effectively to the improvement of living body aging , such as a therapy of various illnesses , such as ischemic diseases , such as the inflammation and the senile dementia it be suppose that active oxygen be involve according to the active oxygen elimination operation which be excellent in the walnut husks extract which be the active principle as mention above , and myocardial infarction , or an allergic disease , a liver failure , and rheumatism , and the skin .
[0020] Moreover, the constituent containing the active oxygen elimination agent of this invention and this can be used effectively also because of prevention of the above-mentioned illness or living body aging. This is because the active oxygen which generated the component which has an active oxygen elimination operation by making it exist beforehand in the living body in the living body can be eliminated quickly and can be detoxified.

[Translation done.]

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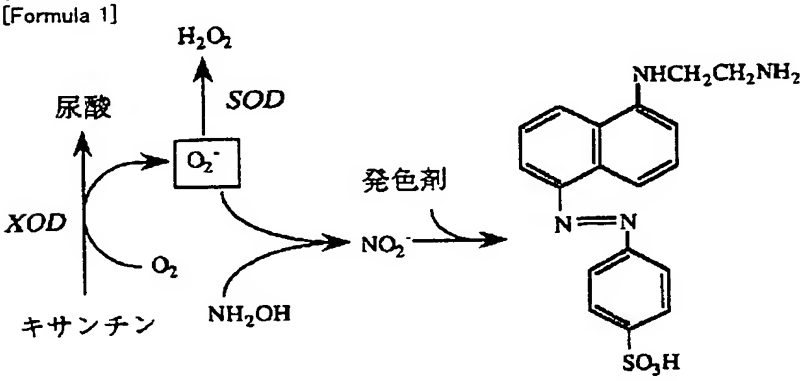
EXAMPLE

[Example] Below, the example of this invention is explained. First, the example of the active oxygen elimination agent of this invention is explained.
[0022]
[Example 1] After having pulverized finely 500g of walnut husks of demon GURUMI, adding 5l. water to this and carrying out heating churning at 105 degrees C for 2 hours, it freeze-dried having filtered, having removed residue and having covered 2 ****s of obtained filtrate, and the walnut husks extract of demon GURUMI was obtained as 4.9g brown powder. This was made into the active oxygen elimination agent as it was.
[0023]
[Example 2] After having pulverized 500g of walnut husks of MANSHUUGURUMI finely, adding 5l. of equivalent mixed liquor of a methanol and n-butyl alcohol to this and performing churning, heating, and reflux for 2 hours, it filtered, residue was removed, vacuum concentration of the obtained filtrate was carried out, and 5.3g was obtained for the walnut husks extract of MANSHUUGURUMI as a viscosity nature liquid. This was made into the active oxygen elimination agent as it was.
[0024]
[Example 3] After having pulverized finely 500g of walnut husks of the Wall nuts, adding 5l. of acetone water solutions to this 50% and performing churning, heating, and reflux for 2 hours, it filtered, residue was removed and vacuum concentration of the obtained filtrate was carried out. Furthermore, freeze-drying processing of this concentrate was carried out over 48 hours, and the walnut husks extract of the Wall nuts was obtained as 5.1g being amorphous. This was made into the active oxygen elimination agent as it was.
[0025] About the active oxygen elimination agent obtained in <evaluation of active oxygen elimination agent> above-mentioned each example, evaluation about safety, an active oxygen elimination operation and aging, a liver failure, and the effectiveness over the allergosis was performed.
[0026] (1) Intraperitoneal [of the 5 weeks old ICR male mouse (weights 25-30g) of every two acute toxicity test 1 groups] was medicated with what dissolved the active oxygen elimination agent obtained in the example 1 in the physiological saline at a rate of 500 mg/kg, 1000 mg/kg, and 2000 mg/kg, respectively, and life and death were judged 14 days after. Consequently, the mouse survived also in said which dose and it was checked that a fifty percent lethal dose value is 2000mg/kg or more. It is clear that the active oxygen elimination agent of this invention excels this in safety.
[0027] (2) Measurement of an active oxygen elimination operation (in vitro)
Based on the reaction formula shown in ** 1, the yield of O2- which was made to generate the superoxide anion (O2-) which is one of the active oxygen by the xanthin-xanthine oxidase (XOD) system, and was generated was measured by the nitrous-acid method, this value was amended with the xanthine oxidase inhibition activity value, and the active oxygen elimination operation value was calculated.
[0028]
[Formula 1]



[0029] 0.1ml of active oxygen elimination agent water solutions which contain the active oxygen elimination agent obtained in each above-mentioned example at a 500microg [/ml] rate could be added to 65mM potassium dihydrogen phosphate, 35mM sodium borate, 0.2ml (henceforth the buffer solution A) of 0.5mMEDTA disodium water solutions, 0.2ml of 0.5mM xanthin solutions, 0.1ml of 10mM hydroxylamine-hydrochloride water solutions, and the mixed liquor of 0.2ml of pure water, they were agitated, and were used as test fluid. Similarly, the solution of the control which used 0.1ml of pure water instead of the active oxygen elimination agent was produced.
[0030] After adding 0.2ml of buffer solutions A which contain xanthine oxidase by 1microl. [/ml] concentration and agitating them in each above-mentioned test fluid and a control solution, the incubation was carried out at 37 degrees C for 30 minutes. 0.2ml of buffer solutions A which do not contain xanthine oxidase in the test fluid and the control solution which were adjusted like the above as a blank was added, and the solution processed like the above was prepared.
[0031] Thus, after adding a 30microMN-1-naphthyl ethylenediamine hydrochloride, 3mM sulfanilic acid, and 2ml of 25% glacial-acetic-acid mixtures to each of each obtained solution and leaving it at a room temperature for 30 minutes, about each solution, the yield of active oxygen was measured with the absorbance in 550nm, and the yield of a uric acid was measured with the absorbance of 295nm.

[0032] Based on the following formulas, the active oxygen elimination activity value was computed using the acquired value. A result is shown in Table 2.
[0033] < active oxygen elimination activity Formula > active oxygen incidence-rate =[for which it asks The notation in (A550-3-A550-4) / (A550-1-A550-2)]x100 uric-acid yield =[(A295-3-A295-4)/(A295-1-A295-2)] x100 active-oxygen elimination activity =100-(active oxygen incidence-rate / uric-acid yield) x100, however a formula It considers as the value of the absorbance of each solution adjusted on the conditions shown in Table 1.
[0034]
[Table 1]

測定波長（nm）		キサンチンオキシダーゼ	
		存在下	非存在下
550（活性酸素量）	コントロール 試験液	A_{550-1} A_{550-3}	A_{550-2} A_{550-4}
295（尿酸量）	コントロール 試験液	A_{295-1} A_{295-3}	A_{295-2} A_{295-4}

[0035]
[Table 2]

	活性酸素消去活性値（%）
実施例1の活性酸素消去剤	67．1
実施例2の活性酸素消去剤	66．2
実施例3の活性酸素消去剤	67．5

It is clear from the above result that the active oxygen elimination agent of this invention has the outstanding active oxygen elimination operation.
[0036] (3) Measurement of an active oxygen elimination operation (in vivo)
After performing blood collecting from a 35-weeks old ICR system MCH male mouse (weights 30-40g), the active oxygen elimination agent obtained in the example 1 was administered orally to this mouse at a rate of 1000 mg/kg. It collected blood after [of administration] 30 minutes, and 2 hours and 5 hours after. The blood serum was picked out from the blood which collected blood with the above-mentioned monograph affair according to centrifugal separation, this was diluted with the buffer solution A 10 times, and active oxygen elimination activity was measured by the same approach as the trial of the above (2). A result is shown in Table 3.
[0037]
[Table 3]

	活性酸素消去活性値（%）
投与前	47．8 ± 15．4
投与30分後	62．9 ± 10．9
2時間後	49．6 ± 7．6
5時間後	58．4 ± 4．5

It is clear for the active oxygen elimination agent of this invention to shift into blood promptly by internal use, and to maintain that effectiveness from this result, for a long time.
[0038] (4) 40 5 weeks old Wister system feminity rats of examination of the effectiveness over aging and a hepatopathy were divided into the appearance which does not have dispersion in weight at four groups, said pellet was made to take in the usual pellet (F2 feed, made in the Funabashi farm) in other three groups, and the active oxygen elimination agent of each example was bred [at one group / the pellet] for 1% of the weight of the blended thing for 24 months to it, respectively. In addition, it enabled it to take in a pellet and water freely to a rat during an experiment.
[0039] After 24-month breeding, it slaughtered, after extracting blood from the rat of each group. Then, the existence of an appearance was observed about disappearance of disseminated depilation, the plumping plasmotomy of the connective tissue under epidermis, sebaceous gland, and a sudoriferous gland as an evaluation index of aging about the rat of each group.
[0040] Furthermore, these rats were dissected, liver was extracted and evaluation about a hepatopathy was performed by observing under a microscope as an upper pathology sample of macro-scopic observation. Moreover, although it reacted easily with unsaturated fatty acid in the living body and peroxylipid was produced when active oxygen occurred in the living body, the

active oxygen elimination effectiveness in each organ was evaluated by measuring the amount of peroxylipid which carried out in this way and was produced to each part of the inside of the body (inside of a blood serum, a brain, and liver) by the TBA method.

[0041] A result is shown [amount / of peroxylipid] in Table 4 as the number of appearance animals about other evaluation criteria as the average of ten animals.
[0042]
[Table 4]

		実施例１	実施例２	実施例３	ｺﾝﾄﾛｰﾙ
過酸化脂質量	血清中	１１	１０	１０	１８
	脳中	２４	２５	２３	２７
	肝臓中	２９	２９	２７	３６
＜老化の評価＞					
散在性脱毛		0	0	0	3
表皮下の結合組織の膨化断裂		0	0	0	4
脂腺、汗腺の消失		0	0	0	2
＜肝障害の評価＞					
肝臓への脂肪沈着		0	0	0	6
肝臓小葉への炎症細胞の湿潤		0	0	0	4
萎縮肝細胞		0	0	0	2

In each organ in the living body, it is clear the active oxygen elimination agent's of this invention to have controlled generation of peroxylipid well by eliminating active oxygen, and to have prevented a living body's aging, and to have prevented the failure of liver.
[0043] (5) According to the guinea pig maximization test method of examination KURIGUMAN of effectiveness to the allergosis, evaluation to an allergic inducement reaction was performed using the cinnamaldehyde which is the sensitizer.
[0044] The following experiments were conducted having made said pellet take in freely 1% of the weight of the thing and water which were blended for the active oxygen elimination agent of each example in other three groups, and breeding a usual pellet (F2 feed, made in the Funabashi farm) and water in them at two groups (among these, one group control group) of the guinea pig of every one groups [8-10], respectively.
[0045] Intradermal injection of 4 times, 1% cinnamaldehyde liquid paraffin solution, the equivalent mixed liquor of Freund's complete adjuvant, 1% cinnamaldehyde liquid paraffin solution, and the 0.05ml of the Freund's complete adjuvant was carried out to the guinea pig of each above-mentioned group except the guinea pig of a control group every two days at every two places of every regions of back. Furthermore, from the injection opening day, the closed patch of what applied the cinnamaldehyde liquid paraffin solution to the putt section of an adhesive bandage 1% was carried out, and dermal administration was also performed at least in the period by the injection end date, and the above-mentioned injection section at coincidence.
[0046] The regions of back of all guinea pigs were shaved after two weeks, injection and a closed patch end date, dermal administration of each cinnamaldehyde liquid paraffin solution of 0.01%, 0.05%, 0.1%, 0.5%, and 1% concentration was carried out by the approach of carrying out a closed patch like the above for 24 hours, and the inducement reaction was seen. The Japanese Dermatological Association this country patch test criteria shown below were used for the criteria of evaluation. A result is shown in Table 5.
[0047] - : Adiaphorous ** : False positive reaction + : Positive reaction ++ : Reaction accompanied by an edema [0048]
[Table 5]

		実施例1	実施例2	実施例3	通常飼料	ｺﾝﾄﾛｰﾙ群
0．01％	－	4／8	4／10	5／9	3／10	9／9
	±	4／8	6／10	4／9	4／10	0／9
	＋	0／8	0／10	0／9	3／10	0／9
	＋＋	0／8	0／10	0／9	0／10	0／9
0．05％	－	4／8	4／10	5／9	2／10	9／9
	±	4／8	6／10	4／9	3／10	0／9
	＋	0／8	0／10	0／9	5／10	0／9
	＋＋	0／8	0／10	0／9	0／10	0／9
0．1％	－	2／8	2／10	3／9	0／10	9／9
	±	4／8	5／10	6／9	4／10	0／9
	＋	2／8	3／10	0／9	5／10	0／9
	＋＋	0／8	0／10	0／9	1／10	0／9
0．5％	－	0／8	0／10	0／9	0／10	9／9
	±	5／8	6／10	8／9	3／10	0／9
	＋	3／8	4／10	0／9	5／10	0／9
	＋＋	0／8	0／10	1／9	2／10	0／9
1％	－	0／8	0／10	0／9	0／10	5／9
	±	4／8	5／10	7／9	0／10	4／9
	＋	4／8	4／10	1／9	5／10	0／9
	＋＋	0／8	1／10	1／9	5／10	0／9

The active oxygen elimination agent of this invention has controlled the good allergic inducement reaction so that clearly from this result.

[0049] Next, the example of constituents, such as food, drugs, etc. containing the active oxygen elimination agent obtained in the above-mentioned example, is explained. In addition, especially all the things in which the loadings used for below do not have a notice are the weight sections.

[0050]

[Examples 4-6] The heating dissolution of the A component was carried out at 150 degrees C among the candy table 6, after casting what made B component homogeneity after addition and churning, it cooled and the candy was manufactured [after cooling at 120 degrees C].

[0051]

[Table 6]

成分		配合量		
		実施例4	実施例5	実施例6
A	砂糖	58．0	67．0	67．0
	水飴	30．0	30．0	30．9
B	クエン酸	1．0	1．0	1．0
	実施例1の活性酸素消去剤	10．0	－	－
	実施例2の活性酸素消去剤	－	1．0	－
	実施例3の活性酸素消去剤	－	－	0．1
	香料	1．0	1．0	1．0

[0052]
[Example 7] B component which the heating dissolution was carried out [component] and carried out the swelling dissolution of the A component of the GUMI table 7 separately at 110 degrees C was added, further, C component was added and it slushed into the mold, and after neglect, it removed from the mold and GUMI was manufactured one whole day and night.
[0053]
[Table 7]

成分		配合量
A	砂糖	40.0
	水飴	45.0
B	ゼラチン	8.0
C	クエン酸	2.0
	実施例3の活性酸素消去剤	4.0
	香料	1.0

[0054]
[Example 8] the component of the juice table 8 — good — agitating — a solution — carrying out — sterilization and aseptic — it sealed and juice was manufactured.
[0055]
[Table 8]

成分	配合量
リンゴ果汁	98.0
実施例1の活性酸素消去剤	2.0

[0056]
[Example 9] The component of the hot cake table 9 was often mixed, it roasted with the frying pan which oiled, and the hot cake was created.
[0057]
[Table 9]

成分	配合量
ホットケーキミックス（市販）	240g
牛乳	180ml
全卵	2個
実施例2の活性酸素消去剤	5g

[0058]
[Example 10] A component of the granule table 10 was often mixed, and in addition, it corned gradually, carrying out kneading of the B component melted in the ethanol water solution 20 100ml% at this. this — 40 degrees C — 2 day-and-night ventilation desiccation — carrying out — screening — the particle size regulation was carried out and it considered as the granule.
[0059]
[Table 10]

成分		配合量
A	乳糖	45
	デキストラン	45
	実施例1の活性酸素消去剤	5
B	ヒドロキシプロピルセルロース	5

[0060]
[Example 11] The component of the injections table 11 was dissolved, and it filtered, and sterilized, and into ampul, aseptic was carried out, and it enclosed, and considered as injections.
[0061]
[Table 11]

成分	配合量
塩化ナトリウム	0.9
実施例3の活性酸素消去剤	0.1
精製水	99.0

[Translation done.]

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CORRECTION OR AMENDMENT

[Kind of official gazette] Printing of amendment by the convention of 2 of Article 17 of Patent Law
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[Procedure revision]
[Filing Date] May 17, Heisei 7
[Procedure amendment 1]
[Document to be Amended] Specification
[Item(s) to be Amended] 0004
[Method of Amendment] Modification
[Proposed Amendment]
[0004] For example, as what is used conventionally, the tocopherol (vitamin E) of lipophilicity, a water-soluble ascorbic acid (vitamin C), etc. are mentioned by the thing of the natural product origin as drugs which have such an operation, and BHT (3, 5-tert-butyl-4-hydroxytoluene), BHA (2(3)-tert-butylhydroxyanisol), etc. are mentioned in a synthetic compound. However, about these drugs, there were problems that an active oxygen elimination operation was not enough and -- there arises carcinogenic misgiving -- by BHT of a synthetic compound, and BHA.
[Procedure amendment 2]
[Document to be Amended] Specification
[Item(s) to be Amended] 0014
[Method of Amendment] Modification
[Proposed Amendment]
[0014] The constituent containing the active oxygen elimination agent of <2> this inventions
The constituent of this invention blends the above-mentioned active oxygen elimination agent according to a conventional method, for example, drugs, food, the charge of makeup, etc. are mentioned.

[Translation done.]

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(54)【発明の名称】　活性酸素消去剤及びこれを含有する組成物

(57)【要約】
【目的】　生体内に発生する活性酸素を十分に消去する作用を有し、且つ安全性が高い活性酸素消去剤及びこれを含有する組成物を提供する。
【構成】　胡桃殻抽出物を活性酸素消去剤として用いる。また、この活性酸素消去剤を食品、医薬品等の組成物に配合する。

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【特許請求の範囲】

【請求項１】　胡桃殻の抽出物からなる活性酸素消去剤。

【請求項２】　前記抽出物が、水、メタノール、エタノール、ｎ－プロピルアルコール、ｉ－プロピルアルコール、ｎ－ブチルアルコール、ｉ－ブチルアルコール、ｓｅｃ－ブチルアルコール、ｔ－ブチルアルコール、アセトンから選ばれる１種又は２種以上で抽出されたことを特徴とする請求項１記載の活性酸素消去剤。

【請求項３】　請求項１記載の活性酸素消去剤を含有する組成物。

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は、活性酸素消去剤及びこれを含有する組成物に関し、詳しくは、胡桃殻の抽出物からなる活性酸素消去剤及びこの活性酸素消去剤を含有する組成物に関する。

【０００２】

【従来の技術】一般的に、活性酸素が生体へ及ぼす影響としては、コラーゲン線維の架橋や、ＤＮＡ螺旋の部分開裂、連鎖的ラジカルの発生による組織の損傷が挙げられ、その結果としてシワや弾力消失といった皮膚や生体の老化、気管支喘息等のアレルギー反応の惹起とヒスタミン放出による炎症の惹起、虚血性疾患のひとつである心筋梗塞における平滑筋の損傷、肝臓障害などの疾患の悪化、また、脳組織の破壊による痴呆の誘発などが引き起こされることが知られている。更に、詳細な原因、機構は不明であるがリューマチの発症にも活性酸素が関与していることも公知の事実である。

【０００３】従って、生体内において活性酸素の発生を抑制することは、これらの疾患を治療あるいは予防する点で非常に重要なことであり、このため、従来より生体内に発生した活性酸素を消去する作用を有する薬剤の探索研究が広く行われてきた。

【０００４】例えば、このような作用を有する薬剤として、従来より用いられているものとしては、天然物由来のものでは、脂溶性のトコフェロール（ビタミンＥ）、水溶性のアスコルビン酸（ビタミンＣ）等が挙げられ、合成化合物では、ＢＨＴ（３，５－ｔｅｒｔ－ブチル－４－ヒドロキシトルエン）、ＢＨＡ（２（３）－ｔｅｒｔ－ブチル－ヒドロキシアニリール）等が挙げられる。しかし、これらの薬剤に関しては、活性酸素消去作用が十分でなく、また合成化合物のＢＨＴ、ＢＨＡでは、発ガン性の疑いが持たれている等の問題があった。

【０００５】また、最近では、十分な薬効と安全性を求めて、生薬抽出物から活性酸素消去作用を有する薬剤を得ようという試みも数多くなされている。例えば、特開昭６０－２２４６２９号、特開昭６１－２４５２２号、特開平２－１９３９３０号、特開平２－２４３６３２号、特開平２－２６４７２７号、特開平３－１５３６２９号、特開平３－２２１５８７号、特開平４－６９３４３号、特開平４－２０２１３８号、特開平４－２４７０１０号など、これらは全て生薬由来物の活性酸素消去作用を利用したものである。しかし、これらの生薬抽出物では、安全性には問題がないものの、活性酸素消去作用の点から言えば、未だ十分なものは得られていなかった。

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【０００６】更に、酵素のひとつスーパーオキサイドデスミューターゼ（ＳＯＤ）を投与することにより、生体内に発生する活性酸素を消去する試みもなされてきているが、ＳＯＤは、タンパク質であるため、その入手が困難であるばかりでなく、消化されてしまうが故に、経口投与は不可能であり、また、注射による投与でも血中半減期が短く満足の行くものではなかった。

【０００７】一方、胡桃の殻については、その粉砕物がスクラブ剤として有用である知見や、その抽出エキスが、皮膚外用剤として保湿性に優れ有用である知見が知られている。しかし、この胡桃殻の抽出エキスが、活性酸素消去作用を有することは知られておらず、また、これを医薬品、食品等に含有させて、上述したような様々な疾患の予防や治療、老化の防止、改善に用いるという試みはされていなかった。

【０００８】

【発明が解決しようとする課題】本発明は、上記観点からなされたものであり、生体内に発生する活性酸素を十分に消去する作用を有し、且つ安全性が高い活性酸素消去剤及びこれを含有する組成物を提供することを課題とする。

【０００９】

【課題を解決するための手段】本発明者らは、上記課題を解決するために、活性酸素消去作用を指標として各種物質をスクリーニングする中で、活性酸素により劣化をうけやすい不飽和油脂を殻の内部に含む胡桃の実が、内部の不飽和油脂を安定に保てるのは、外の殻に何らかの活性酸素に対する防御機構が存在するためではないかと推論し、活性酸素消去剤のスクリーニングに胡桃殻抽出物をかけたところ、この胡桃殻抽出成分に優れた活性酸素消去作用を有する成分が存在することを見出し、本発明を完成するに至った。

【００１０】すなわち、本発明は胡桃殻の抽出物からなる活性酸素消去剤及びこれを含有する組成物に関する。以下、本発明を詳細に説明する。

【００１１】＜１＞本発明の活性酸素消去剤

本発明の活性酸素消去剤は、胡桃殻の抽出物からなる。本発明に用いる胡桃殻とは、一般的に知られている、クルミ科植物の果実の殻であり、例えば、オニグルミ、マンシュウグルミ、ウォールナッツなどの胡桃殻が挙げられる。

【００１２】上記胡桃殻は、活性酸素消去作用を有する成分を含んでおり、抽出により前記成分を含む抽出物を

取り出して、本発明の活性酸素消去剤として用いる。胡桃殻の抽出処理は、連続式、バッチ式等の方法で、常法により冷浸または温浸にて任意の時間行う。例えば、胡桃殻を細かく粉砕し、抽出溶媒に、室温で１～３日間、または抽出溶媒の沸騰温度で１時間～５時間、浸漬し抽出を行う。その後、抽出液から抽出残渣を除いて、減圧または限外濾過を行い抽出物を濃縮する。さらに、必要に応じて有機溶媒を完全に留去して乾固するかまたは凍結乾燥する。

【００１３】このような抽出に用いる溶媒としては、水や各種有機溶媒が挙げられるが、本発明においては特に、水、メタノール、エタノール、ｎ－プロピルアルコール、ｉ－プロピルアルコール、ｎ－ブチルアルコール、ｉ－ブチルアルコール、ｓｅｃ－ブチルアルコール、ｔ－ブチルアルコール、アセトンから選ばれる１種または２種以上が好ましい。

【００１４】＜２＞本発明の活性酸素消去剤を含有する組成物

本発明の組成物は、上記活性酸素消去剤を、常法に従って配合したものであり、例えば、医薬品、食品等が挙げられる。

【００１５】本発明の活性酸素消去剤を医薬品として製剤化する場合、剤型は特に限定されないが、注射剤、散剤、顆粒剤、錠剤、カプセル剤、液剤など通常用いられている各種製剤へ、賦形剤、結合剤、崩壊剤、滑沢剤、着色剤、矯味剤、矯臭剤、増量剤、被覆剤などの医薬品で通常用いられる任意成分とともに、通常の方法に従って剤型化できる。

【００１６】上記医薬品の投与量に関しては、疾患の種類、症状、患者の年齢、体重などにより異なるが、成人１人１日あたり、胡桃殻の抽出物の量として１０ｍｇ～１０００ｍｇを１回ないし数回に分けて経口投与するか、５ｍｇ～５００ｍｇを注射で投与するのが適当である。注射剤の投与方法としては、静脈内投与、動脈内投与、門脈内投与、腹腔内投与、筋肉内投与、皮下投与等が挙げられる。

【００１７】本発明の活性酸素消去剤を食品に配合する場合、特に留意することなく、種々の食品へ、食品で通常用いられている任意成分とともに配合できる。例示をすれば、キャンディーやグミ、ゼリーといったお菓子類やジュースのようなドリンク類、パンなどの主食等が挙げられる。配合量は、食品の種類により異なるが、食品の味を損なわずに、且つ十分な活性酸素消去効果を得るためには、０．１～１０重量％が好ましい。

【００１８】なお、胡桃殻の抽出物は、胡桃が可食果実であることから安全性に優れていることが期待できる。

【００１９】

【作用】本発明の活性酸素消去剤及びこれを含有する組成物は、その有効成分である胡桃殻抽出物の優れた活性酸素消去作用により、上述したように活性酸素が関与しているとされる、炎症、老人性痴呆、心筋梗塞などの虚血性疾患、あるいはアレルギー性疾患、肝臓障害、リューマチなど様々な疾病の治療や皮膚などの生体老化の改善に対して有効に働くものである。

【００２０】また、本発明の活性酸素消去剤及びこれを含有する組成物は、上記疾病や生体老化の予防のためにも有効に使用できる。これは、活性酸素消去作用を有する成分を、あらかじめ生体内に存在させることにより、生体内で発生した活性酸素を素早く消去し、無毒化することができるためである。

【００２１】

【実施例】以下に、本発明の実施例を説明する。はじめに、本発明の活性酸素消去剤の実施例を説明する。

【００２２】

【実施例１】オニグルミの胡桃殻５００ｇを細かく粉砕し、これに５ｌの水を加え、１０５℃で２時間加熱撹拌した後、濾過して残渣を取り除き、得られた濾液を２昼夜かけて凍結乾燥して、オニグルミの胡桃殻抽出物を４．９ｇの褐色粉末として得た。これを、そのまま活性酸素消去剤とした。

【００２３】

【実施例２】マンシュウグルミの胡桃殻５００ｇを細かく粉砕し、これにメタノールとｎ－ブチルアルコールの等量混合液５ｌを加え、撹拌、加熱、還流を２時間行った後、濾過して残渣を取り除き、得られた濾液を減圧濃縮して、マンシュウグルミの胡桃殻抽出物を５．３ｇを粘稠性液体として得た。これを、そのまま活性酸素消去剤とした。

【００２４】

【実施例３】ウォールナッツの胡桃殻５００ｇを細かく粉砕し、これに５０％アセトン水溶液５ｌを加え、撹拌、加熱、還流を２時間行った後、濾過して残渣を取り除き、得られた濾液を減圧濃縮した。更に、この濃縮物を４８時間かけて凍結乾燥処理し、ウォールナッツの胡桃殻抽出物を５．１ｇのアモルファスとして得た。これを、そのまま活性酸素消去剤とした。

【００２５】＜活性酸素消去剤の評価＞上記各実施例で得られた活性酸素消去剤について、安全性、活性酸素消去作用、及び老化、肝臓障害、アレルギー疾患に対する効果に関する評価を行った。

【００２６】（１）急性毒性試験

１群２匹づつの５週齢ＩＣＲ雄性マウス（体重２５～３０ｇ）の腹腔内に、実施例１で得られた活性酸素消去剤を生理食塩水に溶解したものを、それぞれ５００ｍｇ／ｋｇ、１０００ｍｇ／ｋｇ、２０００ｍｇ／ｋｇの割合で投与し、１４日後に生死の判定を行った。その結果、前記何れの投与量においてもマウスは生存し、LD_{50}値は２０００ｍｇ／ｋｇ以上であることが確認された。このことより本発明の活性酸素消去剤が安全性に優れることが明白である。

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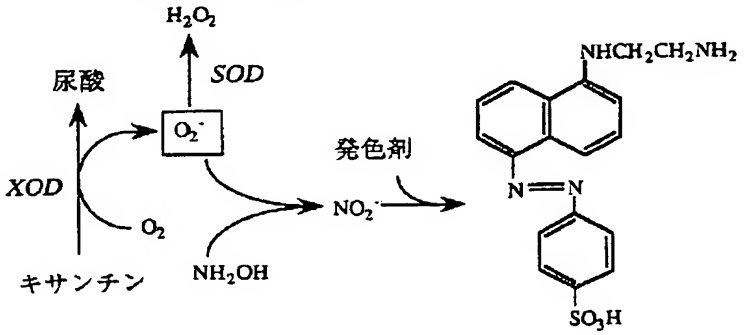
【００２７】（２）活性酸素消去作用の測定（インビトロ）
化１に示す反応式に基づき、キサンチンーキサンチンオキシダーゼ（ＸＯＤ）系により活性酸素のひとつであるスーパーオキシドアニオン（O_2^-）を発生させ、発生し＊たO₂⁻の生成率を亜硝酸法により測定し、この値をキサンチンオキシダーゼ阻害活性値で補正して活性酸素消去作用値を求めた。

【００２８】
【化１】



【００２９】上記各実施例で得られた活性酸素消去剤を５００μｇ／ｍｌの割合で含有する活性酸素消去剤水溶液０．１ｍｌを、６５ｍＭリン酸２水素カリウム、３５ｍＭホウ酸ナトリウム、０．５ｍＭＥＤＴＡ２ナトリウム水溶液（以下、緩衝液Ａという）０．２ｍｌ、０．５ｍＭキサンチン溶液０．２ｍｌ、１０ｍＭヒドロキシルアミン塩酸塩水溶液０．１ｍｌ、純水０．２ｍｌの混合液に、加えてよく撹拌し試験液とした。同様にして、活性酸素消去剤の代わりに純水０．１ｍｌを用いたコントロールの溶液を作製した。

【００３０】上記各試験液及びコントロール溶液に、キサンチンオキシダーゼを１μｌ／ｍｌ濃度で含有する緩衝液Ａを０．２ｍｌ加えて撹拌した後、３７℃で３０分インキュベーションした。ブランクとして、上記と同様に調整された試験液及びコントロール溶液に、キサンチンオキシダーゼを含まない緩衝液Ａを０．２ｍｌ加え、上記と同様に処理した溶液を用意した。

【００３１】このようにして得られた各溶液のそれぞれ※に、３０μＭＮ－１－ナフチルエチレンジアミン塩酸塩、３ｍＭスルファニル酸、２５％氷酢酸混液２ｍｌを加え、３０分間室温で放置した後、各溶液について、５５０ｎｍでの吸光度で活性酸素の発生量を、２９５ｎｍの吸光度で尿酸の発生量を測定した。

【００３２】得られた値を用いて、以下の式に基づき、活性酸素消去活性値を算出した。結果を表２に示す。

【００３３】＜活性酸素消去活性を求める式＞
活性酸素発生率＝［（$A_{550-3}-A_{550-4}$）／（$A_{550-1}-A_{550-2}$）］×１００
尿酸生成率＝［（$A_{295-3}-A_{295-4}$）／（$A_{295-1}-A_{295-2}$）］×１００
活性酸素消去活性＝１００－（活性酸素発生率／尿酸生成率）×１００
但し、式中の記号は、表１に示す条件で調整された各溶液の吸光度の値とする。

【００３４】
【表１】

測定波長（ｎｍ）		キサンチンオキシダーゼ	
		存在下	非存在下
５５０（活性酸素量）	コントロール 試　験　液	A_{550-1} A_{550-3}	A_{550-2} A_{550-4}
２９５（尿酸量）	コントロール 試　験　液	A_{295-1} A_{295-3}	A_{295-2} A_{295-4}

【００３５】　　【表２】

	活性酸素消去活性値（%）
実施例１の活性酸素消去剤	６７．１
実施例２の活性酸素消去剤	６６．２
実施例３の活性酸素消去剤	６７．５

以上の結果から、本発明の活性酸素消去剤が、優れた活性酸素消去作用を有することは明らかである。

【００３６】（３）活性酸素消去作用の測定（インビボ）

３５週齢ＩＣＲ系ＭＣＨ雄性マウス（体重３０～４０ｇ）から採血を行った後、このマウスに実施例１で得られた活性酸素消去剤を、１０００ｍｇ／ｋｇの割合で経口投与した。投与３０分後、２時間後、５時間後に採血を行った。　上記各条件で採血した血液から遠心分離により血清を取り出し、これを、緩衝液Ａで１０倍に希釈して、上記（２）の試験と同様の方法で活性酸素消去活性を測定した。結果を表３に示す。

【００３７】

【表３】

	活性酸素消去活性値（%）
投　与　前	４７．８ ± １５．４
投与３０分後	６２．９ ± １０．９
２時間後	４９．６ ± ７．６
５時間後	５８．４ ± ４．５

この結果から、本発明の活性酸素消去剤は、経口投与により速やかに血中に移行し、長時間その効果を保つことが明白である。

【００３８】（４）老化、肝障害に対する効果の検討

５週齢ウィスター系雌性ラット４０匹を体重にばらつきのない様に４群に分け、１群には通常の固形飼料（Ｆ₂飼料、船橋農場製）を、他の３群にはそれぞれ、各実施例の活性酸素消去剤を前記固形飼料に１重量%の配合したものを摂取させて２４ヶ月飼育した。なお、実験中、ラットには、固形飼料及び水を自由に摂取できるようにした。

【００３９】２４ヶ月飼育後、各群のラットから血液を採取した後、屠殺した。その後、各群のラットについて老化の評価指標として散在性脱毛、表皮下の結合組織の膨化断裂、脂腺、汗腺の消失に関して出現の有無を観察した。

【００４０】更に、これらのラットを解剖して肝臓を摘出し、肉眼観察の上病理標本として顕微鏡下観察することにより肝障害に関する評価を行った。また、生体内に活性酸素が発生すると、体内の不飽和脂肪酸と容易に反応して過酸化脂質を生じるが、このようにして体内各部（血清中、脳中、肝臓中）に生じた過酸化脂質の量をＴＢＡ法で測定することにより、各器官における活性酸素消去効果の評価を行った。

【００４１】結果を、過酸化脂質量については１０匹の平均値として、その他の評価項目については出現匹数として、表４に示す。

【００４２】

【表４】

		実施例１	実施例２	実施例３	ｺﾝﾄﾛｰﾙ
過酸化脂質量	血清中	１１	１０	１０	１８
	脳中	２４	２５	２３	２７
	肝臓中	２９	２９	２７	３６
＜老化の評価＞					
散在性脱毛		０	０	０	３
表皮下の結合組織の膨化断裂		０	０	０	４
脂腺、汗腺の消失		０	０	０	２
＜肝障害の評価＞					
肝臓への脂肪沈着		０	０	０	６
肝臓小葉への炎症細胞の湿潤		０	０	０	４
萎縮肝細胞		０	０	０	２

本発明の活性酸素消去剤は、体内の各器官において、活性酸素を消去することで過酸化脂質の生成をよく抑制し、生体の老化を防ぎ、且つ肝臓の障害を防いでいることが明らかである。

【００４３】（５）アレルギー疾患に対する効果の検討
クリーグマンのモルモットマキシマイゼーションテスト法に準じて、感作物質であるシンナムアルデヒドを用いて、アレルギー性の惹起反応に対する評価を行った。

【００４４】１群８～１０匹づつのモルモットの２群（このうち１群はコントロール群）には通常の固形飼料（F_2飼料、船橋農場製）と水を、他の３群にはそれぞれ、各実施例の活性酸素消去剤を前記固形飼料に１重量％の配合したものと水を、自由に摂取させて飼育しながら以下の実験を行った。

【００４５】コントロール群のモルモットを除いた、上記各群のモルモットに、２日おきに４回、１％シンナムアルデヒド流動パラフィン溶液とフロイントの完全アジュバントの等量混合液、１％シンナムアルデヒド流動パラフィン溶液及びフロイントの完全アジュバントを、各０．０５ｍｌづつ背部の２ヶ所に皮内注射した。更に、注射開始日より注射終了日までの期間、上記注射部位に、１％シンナムアルデヒド流動パラフィン溶液を絆創膏のパット部に塗布したものをクローズドパッチして、経皮投与も同時に行った。

【００４６】注射及びクローズドパッチ終了日の２週間後、すべてのモルモットの背部を剃毛し、０．０１％、０．０５％、０．１％、０．５％、１％濃度の各シンナムアルデヒド流動パラフィン溶液を、上記と同様にクローズドパッチする方法で、２４時間経皮投与して、惹起反応を見た。評価の基準は、以下に示す日本皮膚科学会本邦パッチテスト基準を用いた。結果を表５に示す。

【００４７】－　：　無反応
±　：　疑陽性反応
＋　：　陽性反応
＋＋　：　浮腫を伴う反応

【００４８】
【表５】

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		実施例１	実施例２	実施例３	通常飼料	ｺﾝﾄﾛｰﾙ群
０．０１％	－	４／８	４／１０	５／９	３／１０	９／９
	±	４／８	６／１０	４／９	４／１０	０／９
	＋	０／８	０／１０	０／９	３／１０	０／９
	＋＋	０／８	０／１０	０／９	０／１０	０／９
０．０５％	－	４／８	４／１０	５／９	２／１０	９／９
	±	４／８	６／１０	４／９	３／１０	０／９
	＋	０／８	０／１０	０／９	５／１０	０／９
	＋＋	０／８	０／１０	０／９	０／１０	０／９
０．１％	－	２／８	２／１０	３／９	０／１０	９／９
	±	４／８	５／１０	６／９	４／１０	０／９
	＋	２／８	３／１０	０／９	５／１０	０／９
	＋＋	０／８	０／１０	０／９	１／１０	０／９
０．５％	－	０／８	０／１０	０／９	０／１０	９／９
	±	５／８	６／１０	８／９	３／１０	０／９
	＋	３／８	４／１０	０／９	５／１０	０／９
	＋＋	０／８	０／１０	１／９	２／１０	０／９
１％	－	０／８	０／１０	０／９	０／１０	５／９
	±	４／８	５／１０	７／９	０／１０	４／９
	＋	４／８	４／１０	１／９	５／１０	０／９
	＋＋	０／８	１／１０	１／９	５／１０	０／９

この結果から明らかなように、本発明の活性酸素消去剤は、よくアレルギー性の惹起反応を抑制している。

【００４９】次に、上記実施例で得られた、活性酸素消去剤を含有する、食品、医薬品等の組成物の実施例について説明する。なお、以下に用いる配合量は、特にことわりのないものは、すべて重量部である。

【００５０】

＊【実施例４～６】　キャンディー

表６中、Ａ成分を１５０℃で加熱溶解し、１２０℃に冷却後、Ｂ成分を添加、撹拌後、均一としたものを成型後、冷却してキャンディーを製造した。

【００５１】

【表６】

＊

成分		配合量		
		実施例４	実施例５	実施例６
Ａ	砂糖	５８．０	６７．０	６７．０
	水飴	３０．０	３０．０	３０．９
Ｂ	クエン酸	１．０	１．０	１．０
	実施例１の活性酸素消去剤	１０．０	－	－
	実施例２の活性酸素消去剤	－	１．０	－
	実施例３の活性酸素消去剤	－	－	０．１
	香料	１．０	１．０	１．０

【００５２】　　【実施例７】　グミ

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表７のＡ成分を１１０℃で加熱溶解し、別途膨潤溶解させたＢ成分を添加し、更に、Ｃ成分を添加し、型に流し込み、一昼夜放置後、型からはずしてグミを製造した。

【００５３】

【表７】

成分		配合量
Ａ	砂糖	４０．０
	水飴	４５．０
Ｂ	ゼラチン	８．０
Ｃ	クエン酸	２．０
	実施例３の活性酸素消去剤	４．０
	香料	１．０

【００５４】

【実施例８】　ジュース

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＊表８の成分をよく撹拌して溶液とし、滅菌、無菌充填、密閉してジュースを製造した。

【００５５】

【表８】

成分	配合量
リンゴ果汁	９８．０
実施例１の活性酸素消去剤	２．０

【００５６】

【実施例９】　ホットケーキ

表９の成分をよく混ぜ合わせ、油を引いたフライパンで焼き上げホットケーキを作成した。

【００５７】

【表９】

＊

成分	配合量
ホットケーキミックス（市販）	２４０ｇ
牛乳	１８０ｍｌ
全卵	２個
実施例２の活性酸素消去剤	５ｇ

【００５８】

【実施例１０】　顆粒剤

表１０のＡ成分をよく混合し、これに１００ｍｌの２０％エタノール水溶液に溶かしたＢ成分を練合させながら※

※徐々に加え造粒した。これを４０℃で２昼夜送風乾燥し、篩過、整粒して顆粒剤とした。

【００５９】

【表１０】

成分		配合量
Ａ	乳糖	４５
	デキストラン	４５
	実施例１の活性酸素消去剤	５
Ｂ	ヒドロキシプロピルセルロース	５

【００６０】

【実施例１１】　注射剤

表１１の成分を溶解、濾過、滅菌し、アンプル中へ無菌充填して封入し、注射剤とした。

【００６１】

【表１１】

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成　　分	配 合 量
塩化ナトリウム	０．９
実施例３の活性酸素消去剤	０．１
精 製 水	９９．０

【００６２】

【発明の効果】本発明の活性酸素消去剤およびこれを含有する組成物は、安全性が高く、優れた活性酸素消去作用を有するので、活性酸素が関与するアレルギー疾患、肝障害の予防と治療、生体老化の防止に有効である。

【公報種別】特許法第１７条の２の規定による補正の掲載
【部門区分】第３部門第２区分
【発行日】平成８年（１９９６）１０月８日

【公開番号】特開平７－６９９１２
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【手続補正書】
【提出日】平成７年５月１７日
【手続補正１】
【補正対象書類名】明細書
【補正対象項目名】０００４
【補正方法】変更
【補正内容】
【０００４】例えば、このような作用を有する薬剤として、従来より用いられているものとしては、天然物由来のものでは、脂溶性のトコフェロール（ビタミンＥ）、水溶性のアスコルビン酸（ビタミンＣ）等が挙げられ、合成化合物では、ＢＨＴ（３，５－ｔｅｒｔ－ブチル－４－ヒドロキシトルエン）、ＢＨＡ（２（３）－ｔｅｒｔ－ブチル－ヒドロキシアニソール）等が挙げられる。しかし、これらの薬剤に関しては、活性酸素消去作用が十分でなく、また合成化合物のＢＨＴ、ＢＨＡでは、発ガン性の疑いが持たれている等の問題があった。
【手続補正２】
【補正対象書類名】明細書
【補正対象項目名】００１４
【補正方法】変更
【補正内容】
【００１４】＜２＞本発明の活性酸素消去剤を含有する組成物
本発明の組成物は、上記活性酸素消去剤を、常法に従って配合したものであり、例えば、医薬品、食品、化粧料等が挙げられる。